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PHENYLENE DI ISOTHIOCYANATE (1,4) OR JONIT IN THE TREATMENT OF HOOKWORM INFECTIONS IN UJUNG PANDANG, SOUTH SULAWESI, INDONESIA

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ABSTRACT

Percobaan klinis dengan dosis tunggal dari Jonit (Compound 16842) terhadap 60 penderita cacing tambang telah dilakukan di Ujung Pandang, Sulawesi Selatan.

Penderita tersebut terdiri dari 24 anak-anak dan 36 orang dewasa.

Pemeriksaan tinja dilakukan dengan cara pemeriksaan langsung sediaan basah dan pembiakan larva cara Harada-Mori sebelum dan 2 4 minggu setelah pengobatan.

90 % dari 60 kasus tersebut terkena infeksi dengan Necator americanus, sedang yang 10 % terkena infeksi campuran dengan Necator americanus dan Ankylostoma duodenale.

Pada kelompok pertama terdiri dari penderita berumur antara 5 10 tahun diperoleh penyembuhan parasitologis 81,8 %, pada kelompok kedua terdiri dari penderita berumur antara 11 - 15 tahun diperoleh 92,3 % dan pada kelompok ketiga terdiri dari penderita berumur antara 16 50 tahun diperoleh 86,1 %, sehingga dalam keseluruhan didapatkan penyembuhan 86,7 %. Dalam pada itu ditemukan penurunan hitungan telur rata-rata 85,1 % dan penurunan penetasan rata-rata 93,0 %.

Dengan percobaan ini telah ditunjukkan, bahwa Jonit merupakan obat cacing yang efektip dan aman terhadap pengobatan baik Necator americanus maupun Ankylostoma duodenale.

Efek sampingan seperti mual, murus, muntah, rasa perut tidak enak dan pusing, adalah ringan dan sambil lalu pada hari pertama pengobatan dan tidak membutuhkan pengobatan khusus.

Dalam keseluruhan obat ini nampak dapat diterima baik dengan cara dosis tunggal dan berguna dalam skema pengobatan massal untuk pemberantasan cacing tambang.

INTRODUCTION

Hookworm disease is widespread and is one of the most important diseases of man. It is found nearly in all sub-tropical and tropical countries (warm, moist climate, between 40° Northern and 35° Southern latitude). The number of hookworm infections is probably still near the past estimate of 700 million. (2, 7)

Light infections produce no recognizable symptoms, but the continuous loss of blood in chronic or heavy chronic hookworm infection may give microcytic hypochromic anaemia, and accompanied by malnutrition it may rob energy, weaken the natural protective mechanism of the host and cause many physical and mental problems.

Necator americanus and *Ancylostoma duodenale* are parasites almost exclusively of man. Whenever these infections are endemic, they are the consequence of unsanitary disposal of human feces. It has been found also that of these 2 species each can be encountered epidemiologically as a sole species inhabiting an area or that both of them jointly inhabit the same area.

Ancylostoma duodenale, the Old World hookworm, is prevalent in southern Europe, northern Africa, northern India, China and Japan; it is also found in southern India, Indonesia, Birma, Malaysia, the Philippines, Australia and Paraguay.

Necator americanus, the New World hookworm, is the predominant human hookworm in Asean countries, Polynesia, Micronesia, Melanesia, Central and South Africa, the southern United States, Central and South America. (5)

Jonit (Compound 16842) is the trade name used by Farbwercke Hoechst AG for the substance Phenyl-1, 4-di-iso-thiocyanate, which has

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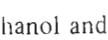
the generic name: Bitoscanate, the molucular formula: $C_8H_4N_2S_2$ and the structural formula: S = C = N –  – N = C = S. Jonit is insoluble in water, soluble in methanol and ethanol and easily soluble in chloroform. It is a white to yellowish-white crystalline, almost odourless, tasteless powder.

LD_{50} of Jonit in mice is 230 mg/kg and in rat 495 mg/kg (micronized substance). 25 mg/kg and 50 mg/kg of the drug daily given for four and a half month did not reveal a leucaemigenic or carcinogenic effects. Jonit cannot yet be regarded perfectly safe for use in children under 3 years of age or in pregnant women. A pronounced effect on the development of the larvae has been found. It has been clearly demonstrated, that Jonit is not only effective against mature worms, but reinfection is not likely to occur for a period of time after treatment. The results have shown, that a considerable amount of drug is absorbed in man (0.0072 ± 0.0036 u mol/ml, 24 hours after a dose of 100 mg/subject). The drug has shown to be effective in animals against Nematodes, Trematodes and Cestodes. It has also been found to be equally effective against *Necator americanus* and *Ancylostoma duodenale*. (3, 4, 9)

The present paper describes our experience with this drug in 60 out-patients suffering from hookworm infection.

MATERIALS AND METHODS

The cases were selected from school-children, students and lecturers of some faculties of the Hasanuddin University.

A total of 304 persons were screened and 60 of them were taken in our study, who had an egg count varying between 500 to 5000 eggs per gram (checked with the McMaster counting method).

The age of the patients ranged from 5 to 50 years. All patients were out-patients.

The diagnoses were made with the direct smear (for one sample 4 smears of each 2 mg fecal matter were made). Testtube cultures according to the Harada-Mori method were made to obtain some index of the frequency of the dominant hookworm species and of the hatching rate (a spread of ½ gram of fecal sample for each testtube).

Follow-up examinations were done 2 to 4 weeks after treatment.

In order to identify the species, the hookworms passed in the stools were collected by sieving one to two days after treatment.

DOSAGE

All patients received medication. The drug, in the form of gelatine capsules each containing 50 mg Jonit, was to be swallowed with water after the evening meal. Coffee or alcoholic beverage should not be taken at the same time, as it might reduce tolerance to the drug.

No measures like fasting, diet or purging were necessary.

The dose schedule for a single dose treatment as recommanded was :

Age	Single dose
3 – 10 years	1 capsule
11 – 15 years	2 capsules
> 16 years	3 capsules

There were 11 patients ranging between 5 – 10 years of age in group I, 13 patients ranging between 11 – 15 years of age in group II and 36 patients ranging between 16 – 50 years of age in group III.

RESULTS

In the first group parasitological cure was achieved in 9 cases out of the 11 cases (81.8 %), while 2 cases remained positive, however with an egg reduction count of 87.6 %, 2 – 4 weeks after treatment. (Table I)

Table 1. Results of a single dose Jonit Treatment in Hookworm infection.

Group	Number of cases	Parasit. Cure Rate		Average % Egg Reduction
		Number	%	
I	11	9	81.8	87.6
II	13	12	92.3	83.4
III	36	31	86.1	84.7
Total	60	52	86.7	85.1

In the second group parasitological cure was obtained in 12 cases out of the 13 cases (92.3 %), while one case remained positive with an egg reduction count of 83.4 %, 2 – 4 weeks after treatment.

In the third group parasitological cure was found in 26 cases out of the 36 cases (86.1 %), while 10 cases remained positive with an egg reduction count of 84.7 %, 2 – 4 weeks after treatment.

The overall parasitological cure rate was 86.7 %, and the average egg reduction count was 85.1 %.

According to the Harada-Mori test 90 % out of 60 cases were infected with *Necator americanus* solely and 10 % had a mixed infection with *Necator americanus* and *Ancylostoma duodenale*. (Table 2)

Table 2. Results of a single dose Jonit treatment in 60 patients with a single and mixed hookworm infection.

Patients		Before treatment with			2-4 weeks after treatment with		
Group	No.	N.a.	N.a. + A.d.	A.d.	N.a.	A.a. + A.d.	A.d.
I	11	10	1	0	2	0	0
II	13	11	2	0	1	0	0
III	36	33	3	0	5	0	0
Total	60	54 (90 %)	6 (10 %)		8 (85.1 %)	0 (100 %)	

N.a. = Necator americanus A.d. = Ancylostoma duodenale

A cure rate of 85.1 % in 54 cases with necatoriasis was achieved. A 100 % cure rate in 10 cases with mixed infection was found; the number of cases however was limited. (Table 2)

An average of 93.0 % hatching rate reduction of hookworm larvae was found in 60 patients after Jonit treatment. (Table 3)

Table 3. Hookworm larvae encountered in 60 patients before and after Jonit treatment according to the Harada Mori test.

Patients		Before treatment larvae of		After treatment larvae of		Hatching Rate Reduction
Group	No.	N.a.	A.d.	N.a.	A.d.	
I	11	249	30	16	0	94.2 %
II	13	240	21	14	0	94.6 %
III	36	481	41	44	0	91.5 %
Total	60	970	92	74	0	93.0 %

Side effects like nausea, diarrhoea, vomiting, abdominal discomfort and dizziness were mild and transient on the first day of treatment and no special treatment was required. (Table 4)

We encountered more *Necator americanus* than *Ancylostoma duodenale* adults in the fecal specimens one to two days after treatment.

Table 4. Side effects with a single dose Jonit treatment (60 cases)

Symptoms	Group I	Group II	Group III	Total	%
Nausea	4	5	6	16	26.6
Diarrhoea	3	3	14	20	33.3
Vomiting	3	3	10	16	26.6
Abdom. discomfort	4	5	6	15	25.0
Dizziness	2	4	7	13	21.6

DISCUSSION

Results obtained in our trial correspond well with those obtained by other investigators, even in cases where other methods, different dosage schedules and fecal examination technique were applied.

Bhandari and Singh in India (1969), using a single dose of 150 mg Jonit treatment, reported a 50 % cure rate with an average of 87 – 91% egg reduction. A dose schedule of 2 X 150 mg Jonit resulted in a 50 % cure rate and an average reduction rate of 75 %, while a 3 X 100 mg dose applied every 24 hours to adults resulted in a 92 % cure rate and a 90 % egg reduction rate.

Mutalik et al., in India (1969) achieved a 50 % cure rate and an average of 77% egg reduction with a dose schedule of 2 X 100 mg Jonit to 5 – 9 years of age patients, a 85% cure rate and an average of 94% egg reduction with a dose schedule of 3 X 100 mg every 24 hours to 10 – 14 years of age patients, and a 74% cure rate and an average of 91% egg reduction with a dose schedule of 3 X 100 mg every 12 hours to patients more than 15 years old.

Sookasen et al., in Thailand (1972) in their clinical trial with a single dose of Jonit obtained a 90% cure rate and a 96.6% egg reduction to patients having 1 – 2000 eggs per gram feces, a cure rate of 50% and an average of 94.2% egg reduction to patients having 2001 – 5000 e.p.g. feces, and a cure rate of 74 % and an average of 88.3 % egg reduction to patients having more than 5000 e.p.g. feces.

O'Holohan et al., in Malaysia (1972) carried out a clinical trial with a single dose of Jonit according to age. They confirmed a 66.6% cure rate with an average of 80 – 90 % egg reduction rate to patients having 1 – 2000 e.p.g. faeces, a 53.8% cure rate with an average of 82 – 90 % egg reduction rate to patients having 2000 – 3000 e.p.g. feces, a 40.0% cure rate with an average of 84 – 90 % egg reduction rate to patients having 3000 – 4000 e.p.g. feces, and a 22.2% cure rate with an average of 95 % egg reduction rate to patients having 5000 – 10,000 e.p.g. faces.

Idris in Jakarta (1976) found a 69% cure rate with and average of 7.31% egg reduction to patients having 1 – 21 e.p.g. feces, a 27 % cure rate with an average of 79.5% egg reduction to patients having 2100 – 5000 e.p.g. feces, and a 44.4% cure rate with an average of 93.3% egg reduction to patients having more than 5000 e.p.g. feces, with a single dose 150 mg Jonit treatment to adult patients.

In general from the above mentioned results can be concluded, that the lesser the egg count the higher cure rate could be achieved. The age/dosage ratio has also to be taken into account. Statements on cure rates can vary due to the possibility of missing a small number of eggs that might be passed after treatment.

The most valuable information on the efficacy of Jonit obtained by the experiment is the high average egg reduction after treatment.

The high cure rates found in necatoriasis and mixed infection have also shown, that Jonit is an effective agent in a single dose regimen, equally effective against *Necator americanus*

and *Ancylostoma duodenale*.

The significantly high average hatching reduction rate in comparison to the average reduction rate, is probably due to the effect of Jonit hampering the development of hookworm eggs or larvae. However, more investigations are needed to verify this.

Diarrhoea was the most common side effect encountered in this trial and most patients appeared to accept it as a visible evidence, that the drug was working to expel the worms.

The result of this clinical trial suggests, that single dose regimens of Jonit would be useful in mass erradi:ation schemes for the control of hookworms.

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